

### REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office Action dated July 2, 2002 are respectfully requested.

#### I. Amendments

##### A. Specification

Typographical errors have been amended, as indicated above.

On page 3, line 2 and page 6, line 23 the definition of "n" has been amended to range from 0-20, as supported by the lipid shown in Fig. 2D.

On page 3, line 3, page 6, line 24, page 7, line 19, and in the abstract, linker, L, when of the form noted in option (i) is amended to agree with the lipid shown in Fig. 1; namely the form  $-X-(C=O)-Y-$ .

##### B. Drawings

Drawings 2A, 2C, 2D, and 3D are amended as discussed above.

##### C. Claims

Claims 19 and 20 stand canceled.

Claims 1, 4, and 30 are amended to define the linking group "L" consistent with the structures shown in the specification. More specifically, the lipid shown in Fig. 1, the imidazole ring is joined to  $-(CH_2)_n-$ , where  $n=2$ . Linking group L is of the form "NH-(C=O)-O". Thus, L corresponds to the embodiment of claim 1 where L is " $-X-(C=O)-Y$ ", wherein X is NH and Y is O. Thus, amendment of option (i) in claim 1 where L is " $-X-(C=O)-Y$ " is supported by Fig. 1.

Claims 1 and 30 are also amended to recite that  $n$  is from 0-20, as supported by the lipid illustrated in Fig. 2D.

#### II. Rejections under 35 U.S.C. §112, second paragraph

Claims 1-18 and 28-33 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the

subject matter. Specifically, the Examiner queries whether the lipid of the formula forms bilayer by itself or whether said lipid is part of the composition.

Independent claim 1 recites "A liposome composition comprising a lipid having the formula...". Independent claim 30 recites "preparing liposomes comprising a lipid having the formula". As is clear from the claim, the liposomes of the claimed composition (claim 1) and of the method (claim 30) need only "comprise" the recited lipid. Nothing in the claim speaks to a requirement that the lipid form bilayers by itself, and the claim covers lipids that fall within the recited structural formula that do spontaneously form lipid bilayers and lipids that do not. For lipids that fall within the recited structural formula and do not form lipid bilayers of their own accord the open ended use of "comprising" permits addition of any other lipid necessary to form liposomes.

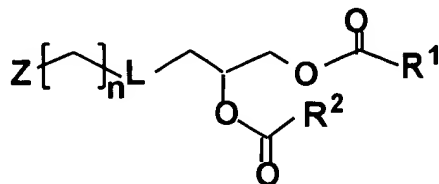
Withdrawal of the rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

### III. Rejections under 35 U.S.C. §102

Claims 1-3, 5-15, and 28-33 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Wolff *et al.* (U.S. Patent No. 5,965,434).

#### A. The Invention

The present invention relates to a liposome composition, and to a method of delivering an agent with the liposomes, comprising a lipid having the formula:



wherein each of R<sup>1</sup> and R<sup>2</sup> is an alkyl or alkenyl chain having between about 8 to about 24 carbon atoms; n = 0-20; L is selected from the group consisting of (i) -X-(C=O)-Y-, (ii) -X-(C=O)-, and (iii) -X-CH<sub>2</sub>-, wherein X and Y are independently selected from oxygen, NH, and a direct bond; and Z is a weakly basic moiety that has a pK of less than about 7.4 and greater than about 4.0.

### B. The Cited Art

WOLFF ET AL. teach lipids of the general form A-B-C (Col. 5, line 5) where A is a hydrophobic moiety (e.g. a lipid), B is a spacer, and C is a cationic, pH-sensitive moiety.

### C. Analysis

The standard for lack of novelty, that is, for anticipation, is one of strict identity. To anticipate a claim for a patent, a single prior source must contain all its essential elements.

#### M.P.E.P. § 2131

The linker moiety of the present invention is of a form selected from (i) -X-(C=O)-Y-, (ii) -X-(C=O)-, and (iii) -X-CH<sub>2</sub>-, wherein X and Y are independently selected from oxygen, NH, and a direct bond.

Wolff *et al.* nowhere show a structure where the linkage between the pH-sensitive group and the hydrophobic moiety is identical to the present linker. None of the structures shown in Wolff *et al.* are identical to the lipid structure presently claimed.

With respect to the generic disclosure by Wolff *et al.* on Col. 5, lines 3-18, the M.P.E.P. § 2131.02 states that "when the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated." "If one of ordinary skill in the art is able to 'at once envision' the specific compound within the generic chemical formula, the compound is anticipated."

The class of substituents for the spacing moiety "B" in Wolff *et al.* is not well delineated, since the class is open ended due to the characterization by Wolff *et al.* of B being "a spacer moiety comprising....". This language leaves the selection of the linking or spacer moiety wide open, permitting the reader to select from the spacers listed by Wolff *et al.* or to select any other spacer not listed by Wolff *et al.* Since Wolff *et al.* in none of the specific embodiments disclosed show a lipid identical to those claimed, it cannot be said that Wolff *et al.* provide guidance or state a preference for

the claimed species. Thus, one of skill in the art, upon reading Wolff *et al.* would not be able to "at once envision" (M.P.E.P. § 2131.02) the compounds presently claimed.

Since Wolff *et al.* fail to disclose a specific embodiment that is identical to the claimed lipid structure, and since "a broad genus does not anticipate a claimed species where one skilled in the art would have to choose judiciously from the dozens of possibilities to arrive at the claimed species" (*In re Kollman et al.*, 201 U.S.P.Q. 193 (C.C.P.A. 1979)), the present claims are not anticipated by Wolff *et al.*

Accordingly, withdrawal of the rejection under 35 U.S.C. §102(e) is respectfully requested.

#### IV. Rejections under 35 U.S.C. §103

Claims 1-15 and 28-33 are rejected under 35 U.S.C. § 103(a) as allegedly upatentable over Wolff *et al.*

Claims 15 and 16 are rejected under 35 U.S.C. § 103(a) as allegedly upatentable over Wolff *et al.* further in view of Allen *et al.* (U.S. Patent No. 6,056,973).

Claims 17 and 18 are rejected under 35 U.S.C. § 103(a) as allegedly upatentable over Wolff *et al.* further in view of Zalipsky *et al.* (U.S. Patent No. 5,395,619).

##### A. The Invention

The invention has been described above.

##### B. The Prior Art

WOLFF ET AL. is discussed above.

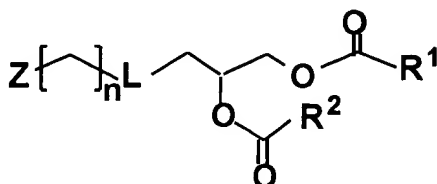
ALLEN ET AL. teach a conjugate of the form "targeting ligand-polymer-lipid".

ZALIPSKY ET AL. describe a lipid-polymer conjugate where a lipid is attached to a hydrophilic polymer.

### C. Analysis

According to the M.P.E.P. §2143.03: "To establish a prima facie case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art."

With respect to the rejection of claims 1-15 and 28-33 over Wolff *et al.*, Wolff *et al.* fail to show a lipid having the formula as claimed. Specifically, none of the lipids shown in Wolff *et al.* show a lipid of the form:



where Z is a weakly basic moiety,  $n=0-20$ , and L is a form selected from (i)  $-X-(C=O)-Y-$ , (ii)  $-X-(C=O)-$ , and (iii)  $-X-CH_2-$ , wherein X and Y are independently selected from oxygen, NH, and a direct bond. A comparison of the claimed lipid with each of the embodiments disclosed by Wolff *et al.* show that none of Wolff *et al.*'s lipid fall within the claims structure.

With respect to the rejection of claims 15 and 16, rejected over a combination of Wolff *et al.* in view of Allen *et al.*, and claims 17 and 18, rejected over a combination of Wolff *et al.* in view of Zalipsky *et al.*, these are patentable over the cited art because if an independent claim is nonobvious under 35 U.S.C. then any claim depending therefrom is nonobvious. (M.P.E.P. § 2143.03). Claims 15-18 are dependent, directly or indirectly, on claim 1, which defines over the cited primary reference to Wolff *et al.* for the reason given above. The secondary references, Allen *et al.* and Zalipsky *et al.* cited for teachings of ligands and polymer chains, do not disclose the missing information from Wolff *et al.* to show all of the present claim limitations. Accordingly, withdrawal of the rejections under 35 U.S.C. § 103 is respectfully requested.

V. Conclusion

In view of the foregoing, the applicant submits that the claims pending in the application comply with the requirements of 35 U.S.C. §112 and patentably define over the cited art. A Notice of Allowance is therefore respectfully requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4302.

Respectfully submitted,

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